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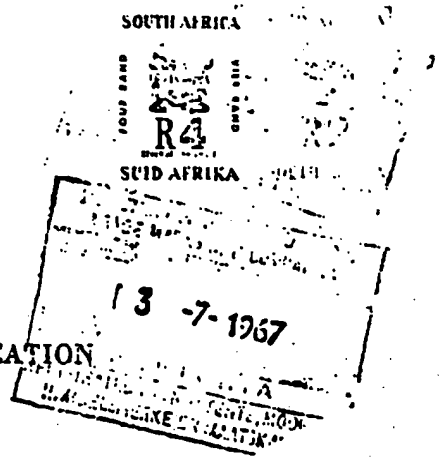

COMPLETE SPECIFICATION

"METHOD OF PREPARING NEW PHARMACOLOGICALLY ACTIVE COMPOUNDS"

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We, N.V. PHILIPS' GLOEILAMPENFABRIEKEN, a limited liability Company organized under the laws of the Kingdom of the Netherlands, and having our seat and office at Emmasingel, EINDHOVEN, Province of North-Brabant, Kingdom of the Netherlands, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained by the following statement:

"Method of preparing new pharmacologically active compounds"

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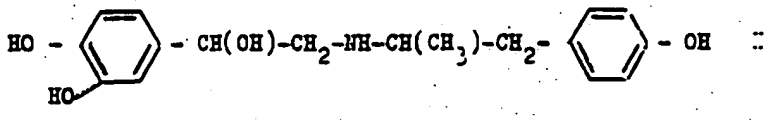
The invention relates to new compounds having interesting pharmacological properties.

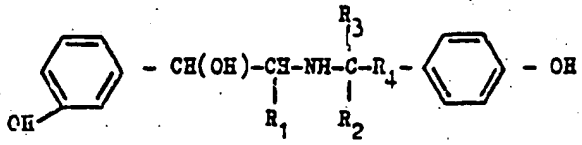
It is known that the compound of formula I



I

hereinafter termed CC 25, has a strong uterospasmolytic and bronchospasmolytic activity.

It was surprisingly found that a group of structurally closely related compounds of formula II

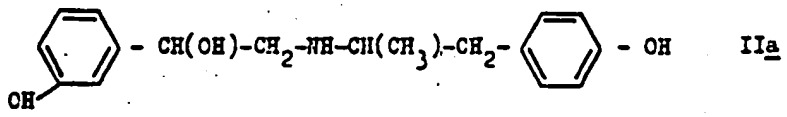


II

and salts thereof have a very strong uterospasmolytic activity the duration of which is a few times larger than that of CC 25 while they have a slight bronchospasmolytic activity. Nor do these compounds have any or substantially any intestinal spasmolytic activities. Therefore these compounds are very specific uterospasmolytics.

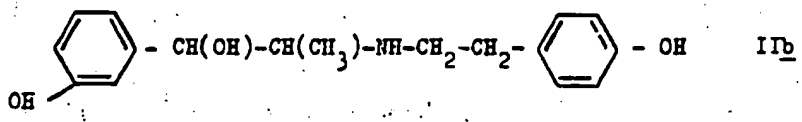
Since the compounds have one or more asymmetric carbon atoms, they have more than one stereochemical configuration. The invention relates to both optical antipodes and racemates and mixtures of racemates of the compounds of formula II and their salts.

A very strong, prolonged activity was found of the β-racemate of the compound of formula IIa, hereinafter termed β-cag 25,



IIa

a compound of which the phenyl acetate has a melting point of 157-158°C, and the phenoxy acetate of 159.5 - 160.5°C, and salts thereof, while in addition the compound of formula IIb



IIb

and its salts should be mentioned by name owing to their activity.

The compounds according to the invention have a few surprising advantages with respect to the known CC 25.

In contrast with CC 25 the compounds according to the invention show no rebound, that is to say: after the compounds have exerted their uterospasmolytic activity: tonus reduction, amplitude and frequency decrease, no increase of the frequency and amplitude of the uterine contractions occurs as compared with the situation prior to the treatment.

The compounds according to the invention have far smaller effects on blood pressure and heart frequency than CC 25. This holds good both for the intensity and the duration of the effect. For example, the intensity of the effect of β-cag 25 is a factor 1/100, the duration a factor 1/10 of that of CC 25.

The toxicity and neurotoxicity of the compounds according to the invention in general is of the same order as that of CC 25. The compounds of formulae IIa and IIb, and their salts, however, are considerably less toxic and neurotoxic.

The new compounds may be characterized as very specific, powerful and long-acting uterospasmolytics having a low toxicity and a very small action on blood pressure and heart frequency.

These properties make the compounds excellently suitable for use, when brought in a suitable mode of application, in the treatment of dysmenorrhea, threatening abortion, partus praematurus and uterine tetanic contractions. The compounds may also be used in animals for example, if the cervix is insufficiently opened as a result of too strong labour pains. In addition the compounds may be used to enlighten embryotomy in animals having a strongly contracted uterus. The compounds may furthermore be used in treating animals having uterine spasms which are the result of an overdose of an oxytosic, in the cesarean section in ruminants, in order to facilitate the introduction into the operation wound of the uterus and in treating animals in which the secundines are removed manually.

The compounds may be administered both orally, intravenously, intramuscularly and rectally.

The way and the frequency of administration of the compounds according to the invention and the dose in which they should be used, vary with the nature and the severity of the disturbances to be treated. In general, the medical attendant will have no difficulty in choosing the correct treatment. When applied to human beings, the compounds will in general be administered in quantities of from to 25 to 250 γ orally, 50 - 100 γ rectally and 5 - 50 γ intravenously. However, it may

oc ur that a dose deviating from the ab ve is sufficient or that a somewhat larger dose is required.

In the veterinary use a quantity of from 0.1 to 0.5 mg/kg will in general be given in the case of intramuscular administration.

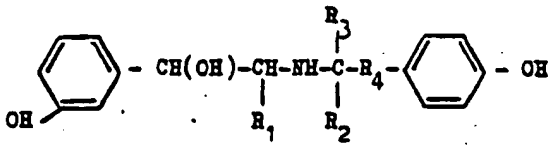
In the above description the term salts is always to be understood to mean acid addition salts formed with pharmaceutically acceptable acids. As such may be mentioned, for example, hydrochloric acid, sulphuric acid, phosphoric acid, hydrobromic acid, sulphamic acid, tartaric acid, citric acid, acetic acid, phenylacetic acid, and phenoxyacetic acid.

The compounds according to the invention may be processed in normal manner to a form suitable for administration to the patient. The compounds may be mixed with or dissolved in solid or liquid carriers commonly used in pharmacy. The mixtures may be processed according to known methods to pharmaceutical compositions, for example, tablets, coated tablets, suppositories, and capsules.

When the compounds are processed to injection liquids, agents for making the liquid isotonic with blood are added. For example, salt may be added or a mixture of water and glycerin may be used.

As solid carriers may be mentioned, for example, starch, talc powder, lactose, gelatin, sodium carboxymethylcellulose, magnesium stearate, saccharose, sec.- and tert.calciumphosphate, casein.

The compounds according to the invention may be prepared according to methods known per se. Therefore the invention relates to a method of preparing new pharmacologically active compounds, characterized in that compounds of formula II



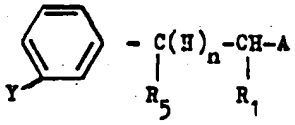
II

in which formula R_1, R_2 and R_3 represent a hydrogen atom or a methyl group and R_4 is a methylene group or an ethylene group, and acid addition salts thereof formed with pharmaceutically acceptable acids, are prepared according to methods which are known for the preparation of such compounds, and according to methods analogous thereto.

The product of the said mode of preparation, if it consists of a mixture of racemates, may be split into these racemates by selective crystallisation, while from racemates the optical antipodes can be obtained by separating the diastereoisomeric salts, formed with an optically active acid, by selective crystallisation.

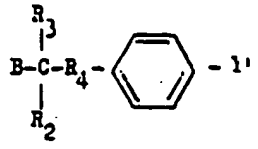
The optical antipodes of the compounds according to the invention may alternatively be obtained by starting in the synthesis from optically active raw materials.

A very suitable method of preparing the compounds of formula II and their salts is that in which a compound of formula III



III

is coupled with a compound of the formula IV



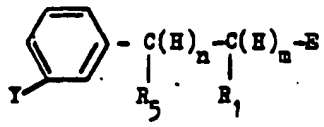
IV

In these formulae, Y and Y' represent a hydroxy group or an etherified or esterified hydroxy group which latter is converted into a free hydroxy group after the coupling reaction by hydrolysis or hydrogenolysis. For the etherification or esterification of the hydroxy groups, lower alcohols and lower acids, respectively, may be used, for example. As such may be mentioned by way of example methanol, benzyl alcohol and diphenyl methyl alcohol and acetic acid and toluene sulphonic acid. R_5 is a hydroxy group or a double-bonded oxygen atom. In the former case n = 1, in the latter case n = 0. The keto group $C-R_5$ may be reduced according to known methods to a carbinol group, for example, by catalytic hydrogenation by means of Ni, Pt or Pd as a catalyst or by reduction with aluminium amalgam and acid or with a metal hydride, for example, $LiAlH_4$ and $NaBH_4$. In these formulae R_1, R_2, R_3, R_4 have the same meanings as in formula II.

In formula III, A is an amino group, in which case B in formula IV is a halogen atom, or is a halogen atom in which case B is an amino group. As a halogen atom is to be considered in particular the bromine atom, but also the chlorine or iodine atom.

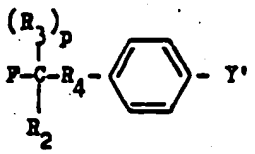
The reaction is preferably carried out in an inert solvent, for example, alcohols, dimethyl formamide, and in the presence of an acid binder. As such may be used an excess of amine. Alternatively, a tertiary amine may be added, for example, triethyl amine and pyridine. The reaction temperature may vary between room temperature and the boiling point of the solvent used.

Compounds of formula II and their salts may also be prepared by coupling a compound of formula V



V

with a compound of formula VI

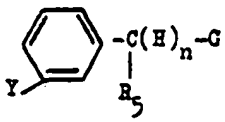


VI

succeeded by reduction.

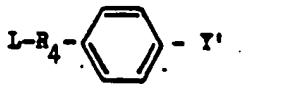
In these formulae Y, Y', R_1, R_2, R_3, R_4, R_5, and n have the same meanings as in formulae III and IV. E represents either a double-bonded oxygen atom, in which case m = 0 and in formula VI F is an amino group and p = 1, or an amino group. In that case m = 1, F in formula VI is a double-bonded oxygen atom and p = 0. This preparation is preferably carried out in a suitable inert solvent. As examples thereof may be mentioned alcohols and ethers. The coupling reaction takes place at temperatures up to the boiling point of the solvent. The formed Schiff base may be reduced in normal manner, for example, by catalytic hydration with Pd, Pt or Ni as a catalyst. Alternatively it is possible to reduce with hydrides, for example, $NaBH_4$ and $LiAlH_4$.

Another method of preparing compounds of formula II and their salts is that in which a compound of the formula VII



VII

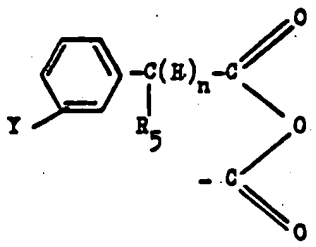
is coupled with a compound of formula VIII



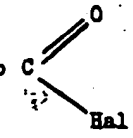
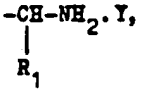
VIII

succeeded by reduction.

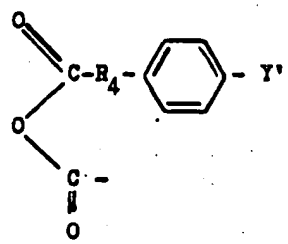
G represents a group of the formula IX,



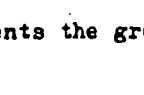
IX

or a group  or a group  . Y, Y', R_1, R_4, and R_5 and n have the above meanings. Hal is a halogen atom.

If G is an aminoalkyl group, L in formula VIII is a carboxyhalide group or a group of formula X,

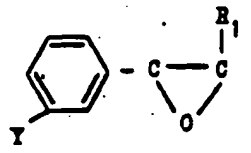


X

while L, in the case G is a carboxylhalide group or a group of the formula IX, represents the group  . This reaction which is preferably carried out in an inert solvent, for example others, ketones, hydrocarbons, may be carried out at room temperature or at elevated temperature. The reaction may be favourably influenced by the presence of an acid binder, for example, sodium acetate, an excess of amine or a tertiary

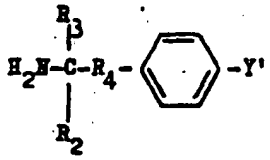
amin , for example, trimethyl amine in pyridine. The carboxylamide group formed may be reduced according to known methods, for example, with $LiAlH_4$.

Alternatively, the compounds of formula II and their salts may be prepared by coupling a compound of formula XI



XI

with a compound of formula XII



XII

in which the symbols have the above described meanings. The reaction may be carried out in suitable solvents, for example, alcohols and ethers. The reaction temperature may as a rule be adjusted between 20 and 100°C.

The invention will be described in greater details with reference to the following examples.

1. 1-(3-hydroxyphenyl)-2-{1-methyl-2-(4-hydroxyphenyl)-ethylamino}-ethanol.

3.90 gms of 2-bromo-3'-methoxyacetophenone were added to a solution of 8.0 gms of 1-methyl-2-(4-methoxyphenyl)-ethylamine in 15 mls of benzene while stirring. As soon as the bromine compound had dissolved stirring was discontinued. After 45 minutes the crystallized hydrobromide of 1-methyl-2-(4-

methoxyphenyl)-ethylamine was sucked off and washed with ether. The filtrate and the wash liquid were combined and shaken with approximately 25 mls of water. After the separation of the water, approximately 20 mls of 2 N hydrochloric acid were added to the solution in benzene/ether, and the whole was thoroughly shaken. As a result of this an oil separated, which after storing for a few days at 0°, crystallized partly. The solid was sucked off, washed with water and ether and then with a mixture of equal parts of acetone and ether as a result of which the hydrochloride of 2-{1-methyl-2-(4-methoxyphenyl)-ethylamino}-3'-methoxyacetophenone was obtained as a substantially white crystalline powder having a melting point of approximately 180-182°C (decomposition).

A solution of 1.50 gms of this hydrochloride in 11 mls of 48 % hydrobromic acid was refluxed for well over 90 minutes. From the solution which was then cooled to 0°, the hydrobromide of 3'-hydroxy-2-{(1-methyl-2-(4-hydroxyphenyl)ethylamino}acetophenone crystallized. Melting point 172-174.5°C (decomposition). This hydrobromide was separated from the solution, washed with little distilled water and then again dissolved, while heating, in approximately 14 mls of distilled water. After the addition of some discolouring carbon the warm solution was filtered and then gradually diluted with totally approximately 12 mls of concentrated hydrochloric acid. As a result of this the hydrochloride of 3'-hydroxy-2-{1-methyl-2-(4-hydroxyphenyl)ethylamino}acetophenone gradually crystallized. After cooling to 0° it was sucked and once again crystallised in the same manner from hydrochloric acid. This hydrochloride melted at approximately 203-205 C (decomposition) and contained 0.5 mol of crystal water. It further had a characteristic UV-spectrum with maxima at 2550 Å (ε 20500) and at 3180 Å (ε 2800).

A suspension of 1.0 gm f this hydrochloride in 25 mls of water was hydrogenated by means of a palladium-on-carbon catalyst at room temperature and approximately 1.1 atm. pressure until the keto group was fully converted into an OH-group. The catalyst was then removed by filtration as a result of which a solution was obtained of the two stereo-isomeric racemates of the hydrochloride of 1-(3-hydroxyphenyl)-2-{1-methyl-2-(4-hydroxyphenyl)ethylamino}ethanol. This substance likewise has a characteristic UV spectrum which differs entirely from that of the starting substance. The maximum lies at 2760 Å (ε approximately 3800) while at 3180 Å no absorption occurs.

2. 1-(3-hydroxyphenyl)-2-{1-methyl-2-(4-hydroxyphenyl)ethylamino}ethanol.

To a solution of 49.2 gms of 3'-benzyloxyacetophenone in 320 mls of methylene chloride a solution of 11.8 mls (34.8 gms) of dry bromine in 80 mls of methylene chloride was added in one time with vigorous stirring. As soon as the reaction set in, the reaction mixture was cooled in an ice bath. As soon as the colour of the bromine had disappeared the formed hydrobromic acid was removed from the pale-yellow solution by the passage of air. The solution was washed neutral with ice water (three portions of 100 mls and three of 50 mls) and then dried on Na_2SO_4. After distilling the solvent in vacuo, the residue was shaken vigorously with 200 mls of petroleum ether (boiling point 40-60°C). As a result of this the 3'-benzyloxy-2-bromoacetophenone crystallized. After sucking off and washing with petroleum ether a white product was obtained with melting point 45-51°C.

13.8 gms of 3'-benzyloxy-2-bromoacetophenone were added to a solution of 25.5 gms of 1-methyl-2(4-benzyloxyphenyl)ethylamine, in 100 mls of benzene, while swirling thoroughly. Swirling was continued until everything had dissolved. After approximately 2 hours, the crystallized hydrobromide was sucked off and washed with benzene. The filtrate was mixed with the wash liquid and then mixed with 50 mls of 2.7 N alcoholic hydrochloric acid. After leaving the mixture to stand overnight at 0°C, the crystallized hydrochloride was sucked off and washed with ethanol. By partly evaporating the filtrate in vacuo, a second quantity of hydrochloride was obtained. These two latter portions were collectively recrystallized from ethanol as a result of which the pure hydrochloride of 3'-benzyloxy-2-{1-methyl-2-(4-benzyloxyphenyl)ethylamino}acetophenone was obtained. Melting point approximately 196-197°C (decomposition).

12.1 gms of this hydrochloride were added to 250 mls of methanol while stirring, after which 6 mls of 4.4 N sodium hydroxide solution and then 2.00 gms of sodium borohydride were added to this suspension. The whole was stirred for some time at room temperature after which 0.4 gm of sodium borohydride was added after one hour. The solution was then left to stand overnight at room temperature. The formed precipitate was sucked off, washed with little ethanol and then with water, after which it was dried. The resulting substance, the 1-(3-benzyloxyphenyl)-2-{1-methyl-2-(4-benzyloxyphenyl)ethylamino}ethanol mainly consisted of one of the two possible stereo-isomeric racemates. By crystallisation from methanol this isomer was obtained in an entirely pure form with melting point 113.5 - 114°C. Melting point of the nitrate 125.5 - 126.5°C. By collectively evaporating partly the filtrate and the wash liquid of the sucked off substance in vacuo, the remainder of the resulting

1(3-benzyl xyphenyl)-2-{1-methyl-2-(4-benzyloxyphenyl)ethyl-amino}ethanol separated as an oil which crystallized after cooling. It was washed a few times with water and dried. The other stereo-isomeric racemate was obtained in a pure form by preparing the nitrate from the mixture of racemates of the last-mentioned crystallized base and crystallizing this from methanol. This nitrate melted at 146-147°C. By adding to a solution hereof in methanol a small excess of 2 N ammonia the base of this isomer precipitated which, after crystallisation, melted at 94.5 - 95.5°C and contained some crystal water or alcohol.

By hydrating a warm solution of 4 gms of the base with melting point of 113.5 - 114°C in 100 mls of ethanol after the addition of the equivalent quantity of dilute hydrochloric acid and a palladium-on-activated-carbon catalyst under the circumstances mentioned in the previous example, the two benzyl groups were split off hydrogenolytically and a solution was obtained of the hydrochloride of one of the two possible racemates of 1-(3-hydroxyphenyl-2-{1-methyl-2-(4-hydroxyphenyl)ethylamino}ethanol.

By adding to this solution an equivalent quantity of dilute ammonia the base precipitated as a tough mass, which crystallized after some time. Melting point 162-163°C. The substance had a characteristic UV-absorption spectrum as mentioned in example I for this substance. Of this base the phenyl acetate was prepared. Melting point 142-143°C.

In a similar manner the other stereo-isomeric racemate of 1-(3-hydroxyphenyl)-2-{1-methyl-2-(4-hydroxyphenyl)ethylamino}-ethanol was obtained from the base of 1(3-benzyloxyphenyl)-2-{1-methyl-2-(4-benzyloxyphenyl)ethylamino}ethanol with melting point 94.5 - 95.5 C. The phenyl acetate of this stereo-isomer

melted from 157-158 C. The UV-absorption spe trum c rresponded t that f the other isomer.

3. 1-(3-hydroxyphenyl)-2-{1-methyl-2-(4-hydroxyphenyl) ethylamino}ethanol.

By hydrogenating a solution of the hydrochloride of 3'-benzyloxy-2-{1-methyl-2-(4-benzyloxyphenyl)ethylamino}acetophenone obtained in example 2 in ethanol in the manner described in examples 1 and 2 until the substance had reacted with 3 mol of hydrogen per mol, a solution of the two stereo-isomeric racemates of the hydrochloride of 1-(3-hydroxyphenyl)2-{1-methyl-2-(4-hydroxyphenyl)ethylamino}ethanol was obtained with the same physical properties as mentioned in example 1.

4. 1-(3-hydroxyphenyl)-2-{1,1-dimethyl-2-(4-hydroxyphenyl) ethylamino}ethanol.

15.5 gms of 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine were dissolved in 50 mls of absolute ethanol. After the addition of 8.70 gms of 3'-benzyloxy-2-bromoacetophenone the solution was shaken vigorously until everything had dissolved. After 90 minutes the crystallized substance was sucked off, washed four times with 25 mls of ether and two times with 25 mls of water and then dried. The resulting product was 3'-benzyloxy-2{1,1-dimethyl-2-(4-methoxyphenyl)ethylamino}acetophenone. After separating the formed hydrobromide of 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine and adding hydrochloric acid, a second portion of coupling product as hydrochloride could be obtained from the filtrate. It had a characteristic UV-absorption spectrum with maximum absorptions at 2545 Å and 3130 Å (ε 10700 and 2700

respectively).
It melted at 159-167.5°C (decomposition).

3.95 gms of the aminoketone were suspended in 40 mls of methanol and dissolved as hydrochloride by the addition of 2.2 mls of 4.4 N ethanolic hydrochloric acid. After the addition of a palladium-on-active-carbon catalyst the solution was hydrogenated. After one equivalent of hydrogen had been taken up, the reaction was interrupted, the catalyst was sucked off and washed with methanol. The filtrate was evaporated in vacuo to a volume of 4.7 gms. The 3'-hydroxy-2-{1,1-dimethyl-2-(4-methoxyphenyl)ethylamino}acetophenone hydrochloride crystallized from the resulting mixture and could be obtained in a pure form by sucking off and washing with acetone; melting point 193-197°C (decomposition). The UV-absorption spectrum shows maxima at 2550 Å and 3160 Å with ε 10300 and 2700 respectively.

The above-described mixture (4.7 gms) was demethylated with 25 mls of boiling 48 % of hydrobromic acid in one hour. The still warm solution was decanted from the formed tar. After cooling and removing the precipitated tar, the hydrobromide of the 3'-hydroxy-2-{1,1-dimethyl-2-(4-hydroxyphenyl)ethylamino}acetophenone crystallized. This hydrobromide was converted into the hydrochloride by dissolving in hot water succeeded by gradual dilution with concentrated hydrochloric acid (decomposition point 242-245°C). From the precipitated tar another quantity of the hydrochloride could be obtained by extraction with hot water succeeded by dilution with concentrated hydrochloric acid.

To a suspension of 0.29 gm of the hydrochloride of 3'-hydroxy-2-{1,1-dimethyl-2-(4-hydroxyphenyl)ethylamin}acetophenone in a

mixture of 5 mls of water and 5 mls of ethanol a palladium-on-activ -carb n catalyst was added obtained by reduction of 0.6 ml of 10 % $PdCl_2$ solution and 0.06 g of carbon. The mixture was hydrogenated until the keto group was converted into a carbinol group. The catalyst was filtered off and washed with methanol and water. The filtrate and the wash liquid were evaporated in vacuo until a residue of 0.48 gm was obtained. By the addition of 28.5 mls of water and 0.50 ml of 0.1 NaOH, a 1 % solution of 1-(3-hydroxyphenyl)-2-{1,1-dimethyl-2-(4-hydroxyphenyl)ethyl-amino}ethanol hydrochloride was obtained with pH 6. The characteristic UV-absorption spectrum of the substance in this solution showed a maximum at 2750 Å (ε 3600) and consequently corresponded to that of its analogue of example 1. The 3,5-dinitrobenzoate melted at 232-235°C (decomposition).

5. 1-(3-hydroxyphenyl)-2-{1-methyl-3-(4-hydroxyphenyl)propylamino}ethanol.

9.3 gms of 3'-benzyloxy-2-bromoacetophenone were added to a solution of 12.5 gms of 1-methyl-3-(4-methoxyphenyl)propylamine in 50 mls of benzene. The mixture was vigorously shaken, the bromine compound dissolved and the 1-methyl-3-(4-methoxyphenyl) propylamine hydrobromide began to precipitate. After 25 minutes the precipitate was sucked off and washed with ether. To the filtrate and the wash ether 9 mls of 4.4 N ethanolic hydrochloric acid were added. After the addition of 10 mls of water and another 250 mls of ether, the hydrochloride of 3'-benzyloxy-2-{1-methyl-3-(4-methoxyphenyl)propylamino}acetophenone crystallized.

1.96 gms of the hydrochloride of the above aminoketone were added to 25 mls of 48 % hydrobromic acid. The mixture was boiled

for 15 minutes. After cooling, the solution was decanted from the precipitated oil after which the hydrobromide of 3'-hydroxy-2-{1-methyl-3-(4-hydroxyphenyl)propylamino}acetophenone crystallized. The hydrochloride of 3'-hydroxy-2-{1-methyl-3-(4-hydroxyphenyl)propylamino}acetophenone was obtained from the precipitated oil by extraction with warm water and the gradual addition of concentrated hydrochloric acid to the extract. The hydrobromide and the hydrochloride were together dissolved in 10 mls of hot water and the solution was decoloured with active carbon. The carbon was filtered off, washed two times with 2.5 mls of hot water after which 2 mls of concentrated hydrochloric acid were added to the filtrate. The hydrochloride crystallized. After repeating this process two times, the hydrochloride was obtained in a pure form. The substance had a decomposition point of 217-223°C and a characteristic UV-absorption spectrum with maxima at 2545 Å and 3130 Å (ε 9590 and 2600, respectively).

To a suspension of 0,48 gms of this hydrochloride in 20 mls of 50 % methanol a palladium-on-active-carbon catalyst was added and the mixture was hydrogenated until the keto function was fully converted into an alcohol function. The catalyst was filtered off and washed with methanol and water. The filtrate and the wash liquid were evaporated *in vacuo* until a residue of 1.07 gms was obtained. Of this residue the solvent was entirely removed by freeze-drying at 0.02 mm. By dissolving this residue (0.51 gm) in 48 mls of water, a 1 % solution of 1-(3-hydroxyphenyl)-2-{1-methyl-3-(4-hydroxyphenyl)propyl-amino}ethanol hydrochloride with pH 5 was obtained. The characteristic form of the UV absorption spectrum of the substance in this solution corresponded to that of its analogue of example 1.

6. 1-(3-hydroxyphenyl)-2-{2-(4-hydroxyphenyl)ethylamino} propanol.

3.35 gms of 2-(4-benzyloxyphenyl)ethylamine hydrochloride in 5 mls of absolute ethanol were converted into the base by the addition of a sodium ethanolate solution obtained from 0.29 gm of sodium and 5 mls of absolute ethanol. After removing the precipitated sodium chloride by filtration, 2,2 mls of triethylamine and 4.08 gms of 3'-benzyloxy-2-bromopropiophenone were added. The mixture was refluxed for 3 hours and then evaporated in vacuo to 9 gms. After the addition of 30 mls of water and 60 mls of ether, a small quantity of undissolved hydrobromide was sucked off from the reaction product. The layers in the filtrate were separated; the ether layer was washed with 15 mls of water and the water layer was washed with 15 mls of ether. The ether layer was then acidified with 6 mls of 4 N hydrochloric acid. The resulting hydrochloride of 3'-benzyloxy-2-{2-(4-benzyloxyphenyl)ethylamino}propiophenone crystallized, was sucked off and purified by crystallisation from a mixture of water-ethanol (1 : 2). The substance melted at 209-213°C (decomposition) and had a UV-absorption spectrum with maxima of 2565 and 3120 Å with ε 10200 and 2500, respectively.

2.51 gms of this hydrochloride were suspended in 120 mls of 80 % methanol. After the addition of 2.5 mls of 1 % $PdCl_2$ solution and 0.25 gm of decolouring carbon the mixture was hydrogenated until the keto compound was reduced to the [illegible]. The catalyst was sucked off and washed with water and methanol and the filtrate was evaporated in vacuo to a residue of 2 gms. The residue was dissolved in 10 mls of absolute ethanol and

diluted with 50 mls of ether. The hydrochl ride of 1-(3-hydroxyphenyl)-2-{2-(4-hydroxyphenyl)ethylamino}propan 1, crystallized with some crystal water, melting point 182.5 - 189°C (anhydrous). The substance has a characteristic UV-absorption spectrum with a maximum at 2750 Å with ε = 3660.

7. Preparation tablet.

25 mgs of the β-racemate of 1-(3-hydroxyphenyl)-2-{1-methyl-2-(4-hydroxyphenyl)ethylamino}ethanol phenylacetate were mixed with 40 gms of starch and 10 gms of lactose. The mixture was wetted with a solution of 0.5 gm of polyvinylpyrrolidone in a little ethanol. The resulting mass was granulated and dried at 40 to 80°C. The granulate was then crushed and mixed with 4.5 gms of formaldehyde-casein, 4 gms of carboxymethylcellulose and 1 gm of magnesium stearate. The resulting mass was tabletted to 70-mgs tablets.

8. Preparation coated tablet.

The tablet prepared according to example 7 was processed in normal manner to a 140-mgs coated tablet by providing a sugar coating.

9. Composition suppository.

50 γ of 1-(3-hydroxyphenyl)-2-{2-(4-hydroxyphenyl)ethylamino}propanol

350 mgs of tert. calcium phosphate.

550 mgs of saccharose.

150 mgs of maize starch.

40 mgs of talcum.

10 mgs of magnesium stearate.

400 mgs of suppository mass.

10. Composition injection liquid.

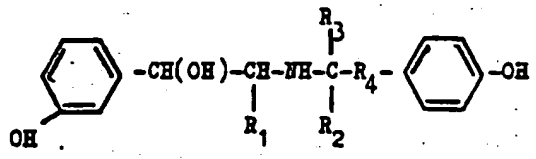
10 γ of 1-(3-hydroxyphenyl)-2-{2-(4-hydr xyphenyl) ethylamino}propanol.HCl.

15 mgs of benzyl alcohol.

1 ml of pyrogen-free distilled water.

Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:

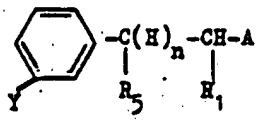
1. A method of preparing new pharmacologically active compounds, characterized in that compounds of formula II



II

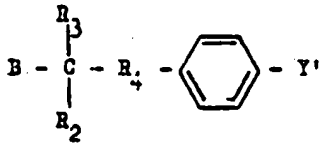
in which formula R_1, R_2 and R_3 represent a hydrogen atom or a methyl group and R_4 is a methylene or an ethylene group, and acid addition salts thereof formed with pharmaceutically acceptable acids, are prepared according to methods which are known for the preparation of such compounds and according to methods analogous thereto.

2. A method as claimed in claim 1, characterized in that a compound of the formula III



III

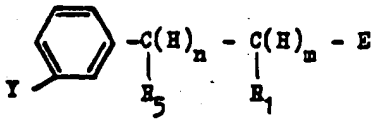
in which formula Y represents a hydroxy group or an etherified or esterified hydroxy group, n = 0 or 1, R_5 a hydroxy group if n = 1 and a double-bonded oxygen atom if n = 0, R_1 is a hydrogen atom or a methyl group and A is an amino group or a halogen atom is coupled with a compound of formula IV,



IV

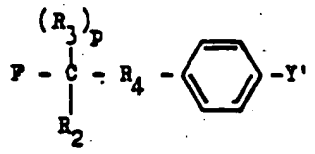
in which formula R_2, R_3 and R_4 hav the same meanings as in formula II, Y' has the same meaning as Y in formula III and in which B, in the case A in formula III is an amino group, is a halogen atom, and, in the case A is a halogen atom, is an amino group, etherified or esterified hydroxy groups represented by Y and Y', are converted into free hydroxy groups and a keto group C-R_5 is reduced to a carbinol group.

3. A method as claimed in claim 1, characterized in that a compound of formula V



V

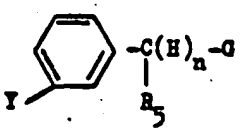
in which formula Y, R_1, R_5 and $\underline{n}$ have the same meanings as in formula III and E represents a double-bonded oxygen atom, in which case m = 0 or an amino group, in which case m = 1, is coupled to a compound of formula VI



VI

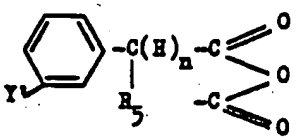
in which formula R_2, R_3, R_4 and Y' have the same meaning as in formula IV and in which F, if E in formula V is a double-bonded oxygen atom, represents an amino group in which case p = 1, and a double-bonded oxygen atom if E represents an amino group, in which case p = 0, the Schiff base formed during the coupling and a keto-group C-R_5 is reduced and etherified or esterified hydroxy groups Y and Y' are converted int free hydroxy gr ups.

4. A method as claimed in claim 1, characterized in that a compound of formula VII



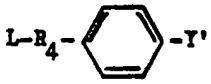
VII

in which formula Y, R_5 and n have the same meanings as in formula III and wherein G represent a group $-CH-NH_2$ (with R_1) or a group $-C(=O)-Hal$ or a group of formula IX:



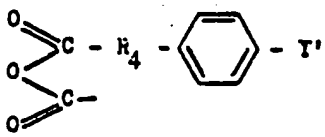
IX

in which groups the symbols have the same meanings as in formula III and Hal represents an halogen atom, is coupled with a compound of formula VIII,



VIII

in which formula R_4 and Y' have the same meanings as in formula IV and L represents a group $H_2N-C(R_3)(R_2)-$ in case G in formula VII is a group $-C(=O)-Hal$ or a group of formula IX or a group of $Hal-C(=O)-$ or a group of formula X.

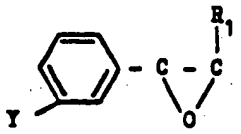


X

in case G is a group $CH-NH_2$ (with R_1), in which the symbols used have the

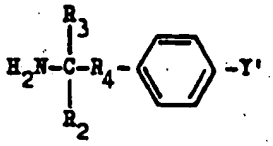
same meaning as in formula IV and, after the coupling reaction, the amido group and keto group C-R_5 are reduced and etherified or esterified hydroxy groups Y and Y' are converted into free hydroxy groups.

5. A method as claimed in claim 1, characterized in that a compound of formula XI



XI

in which formula R_1 and Y have the same meanings as in formula III, is coupled to a compound of formula XII,



XII

in which formula R_2, R_3, R_4 and Y' have the same meanings as in formula IV and etherified and esterified hydroxy groups are converted into free hydroxy groups.

6. A method as claimed in any of claims 1 to 5, characterized in that a mixture of racemates is separated into racemates by selective crystallisation.

7. A method as claimed in any of the preceding claims, characterized in that 1-(3-hydroxyphenyl)-2-{1-methyl-2-(4-hydroxyphenyl)ethylamino}ethanol and acid addition salts are prepared with pharmacologically acceptable acids thereof.

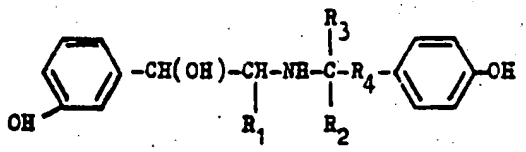
8. A method as claimed in any of the claims 1 to 6, characterized that 1-(3-hydroxyphenyl)-2-{1,1-dimethyl-2-(4-hydroxyphenyl)ethylamino}ethanol and acid addition salts

are prepared with pharmacologically acceptabl acids thereof.

9. A method as claimed in any of the claims 1 to 6, characterized in that 1-(3-hydroxyphenyl)-2-{1-methyl-3-(4-hydroxyphenyl)propylamino}ethanol and acid addition salts are prepared with pharmacologically acceptable acids thereof.

10. A method as claimed in any of the claims 1 to 6, characterized in that 1-(3-hydroxyphenyl)-2-{2-(4-hydroxyphenyl)ethylamino}propanol and acid addition salts are prepared with pharmacologically acceptable acids thereof.

11. Compounds of formula II



II

in which formula R_1, R_2 and R_3 represent a hydrogen atom or a methyl group and R_4 is a methylene group or an ethylene group and salts thereof with pharmacologically acceptable acids.

12. 1-(3-hydroxyphenyl)-2-{1-methyl-2-(4-hydroxyphenyl)ethylamino}ethanol and acid addition salts thereof with pharmacologically acceptable acids.

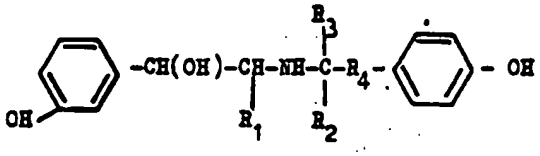
13. 1(3-hydroxyphenyl)-2-{1,1-dimethyl-2-(4-hydroxyphenyl)ethylamino}ethanol and acid addition salts thereof with pharmacologically acceptable acids.

14. 1-(3-hydroxyphenyl)-2-{1-methyl-3-(4-hydroxyphenyl)propylamino}ethanol and acid addition salts thereof with pharmacologically acceptable acids.

15. 1-(3-hydroxyphenyl)-2-{2-(4-hydroxyphenyl)ethylamino}propanol and acid addition salts thereof with pharmacologically acceptable acids.

16. The β-racemate of 1-(3-hydroxyphenyl)-2-{1-methyl-2-(4-hydroxyphenyl)ethylamino}ethanol and acid addition salts thereof with pharmacologically acceptable acids.

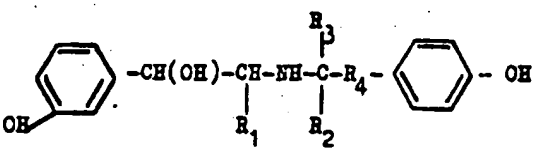
17. A method of preparing pharmaceutical and veterinary compositions, characterized in that a compound of formula II



II

in which formula R_1, R_2 and R_3 represent a hydrogen atom or a methyl group and R_4 is a methylene group or an ethylene group and acid addition salts thereof with pharmacologically acceptable acids are brought into a therapeutically suitable form of administration.

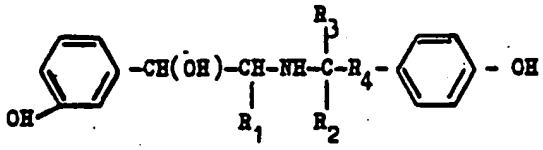
18. A method of preparing pharmaceutical and veterinary compositions, characterized in that a compound of formula II



II

in which formula R_1, R_2 and R_3 represent a hydrogen atom or a methyl group and R_4 is a methylene group or an ethylene group, and acid addition salts thereof with pharmacologically acceptable acids are mixed with or dissolved in solid or liquid carriers.

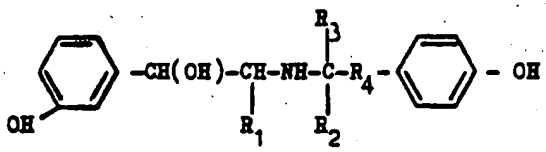
19. Pharmaceutical and veterinary compositions characterized by a content of a compound of formula II.



II

in which formula R_1, R_2 and R_3 represent hydrogen or methyl and R_4 is methylene or ethylene, or an acid addition salt thereof with a pharmacologically acceptable acid.

20. Pharmaceutical and veterinary compositions having a content of a compound of formula II



II

in which formula R_2 and R_3 represent hydrogen or methyl and R_4 represents methylene or ethylene, or an acid addition salt thereof with a pharmacologically acceptable acid.

21. A composition as claimed in claim 19 or 20, characterized by a content of 1-(3-hydroxyphenyl)-2-{1-methyl-2-(4-hydroxyphenyl)ethylamino}ethanol or an acid addition salt thereof with a pharmacologically acceptable acid.

22. A composition as claimed in claim 19 or 20, characterized by a content of 1-(3-hydroxyphenyl)-2-{1,1-dimethyl-2-(4-hydroxyphenyl)ethylamino}ethanol or an acid addition salt thereof with a pharmacologically acceptable acid.

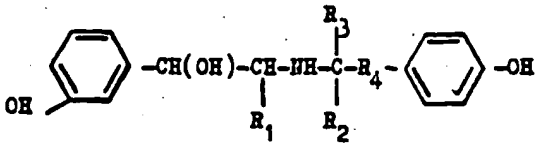
23. A composition as claimed in claim 19 or 20, characterized by a content of 1-(3-hydroxyphenyl)-2-{1-methyl-3-(4-hydroxyphenyl)propylamino}ethanol or an acid addition salt thereof with a pharmacologically acceptable acid.

24. A composition as claimed in claim 19 or 20, characterized by a content of 1-(3-hydroxyphenyl)-2-{2-(4-hydroxyphenyl

ethylamino}propanol and an acid addition salt thereof with a pharmacologically acceptable acid.

25. A composition as claimed in claim 19 or 20, characterized by a content of the β-racemate of 1-(3-hydroxyphenyl)-2-{1-methyl-2-(4-hydroxyphenyl)ethylamino}ethanol and acid addition salts thereof with pharmacologically acceptable acids.

26. A method of treating human beings or animals, characterized in that a compound of formula II



II

or an acid addition salt thereof with a pharmacologically acceptable acid is administered.

27. A method of preparing new pharmacologically active compounds, substantially as herein described with reference to the specific examples.

28. Pharmaceutical and veterinary compositions, substantially as herein described with reference to the specific examples.

29. Compounds whenever prepared by the method as claimed in any one of claims 1 to 10 inclusive or in claim 27.

30. A method of preparing pharmaceutical and veterinary compositions substantially as described herein.

31. Compositions whenever prepared by the method as claimed in claim 17 or claim 18 or claim 30.

Dated this 3rd day of July, 1967.

PATENT ATTORNEY.